AAPS Transporter Workshop

March 8, 2005, Parsippany, NJ

An FDA view of Drug Transporters & What Could be included in a Submission

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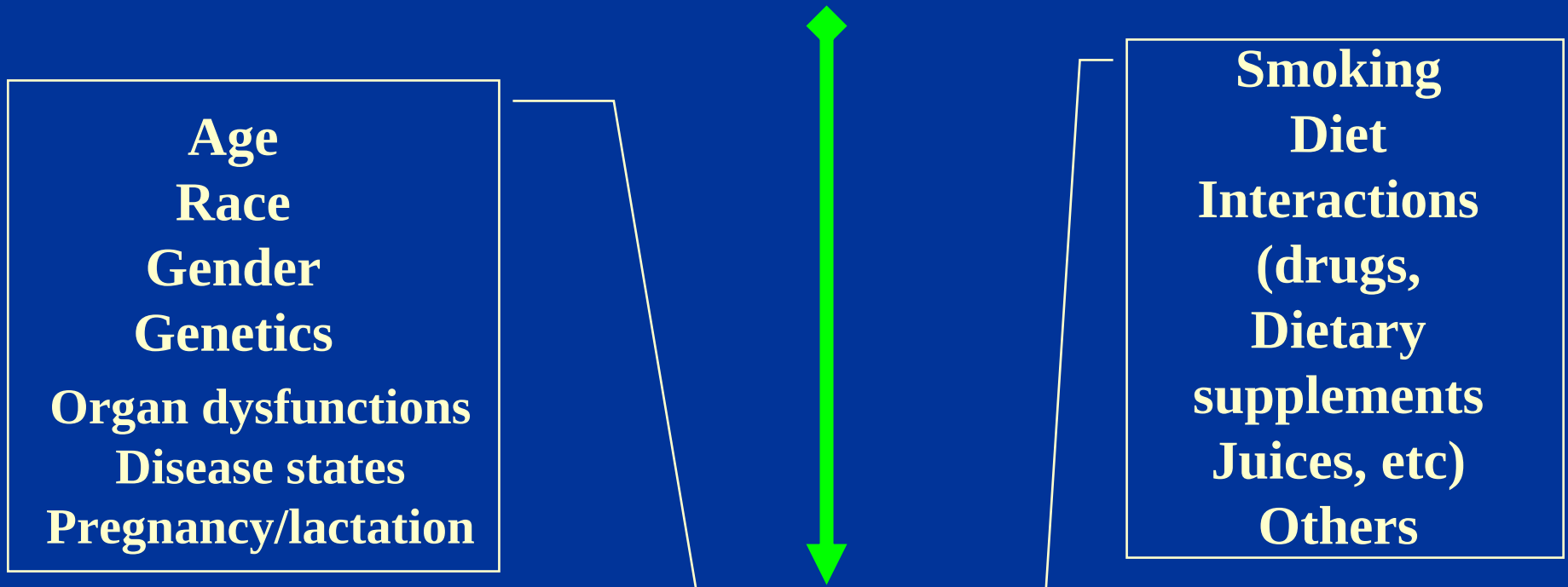
Center for Drug Evaluation and Research

Food & Drug Administration

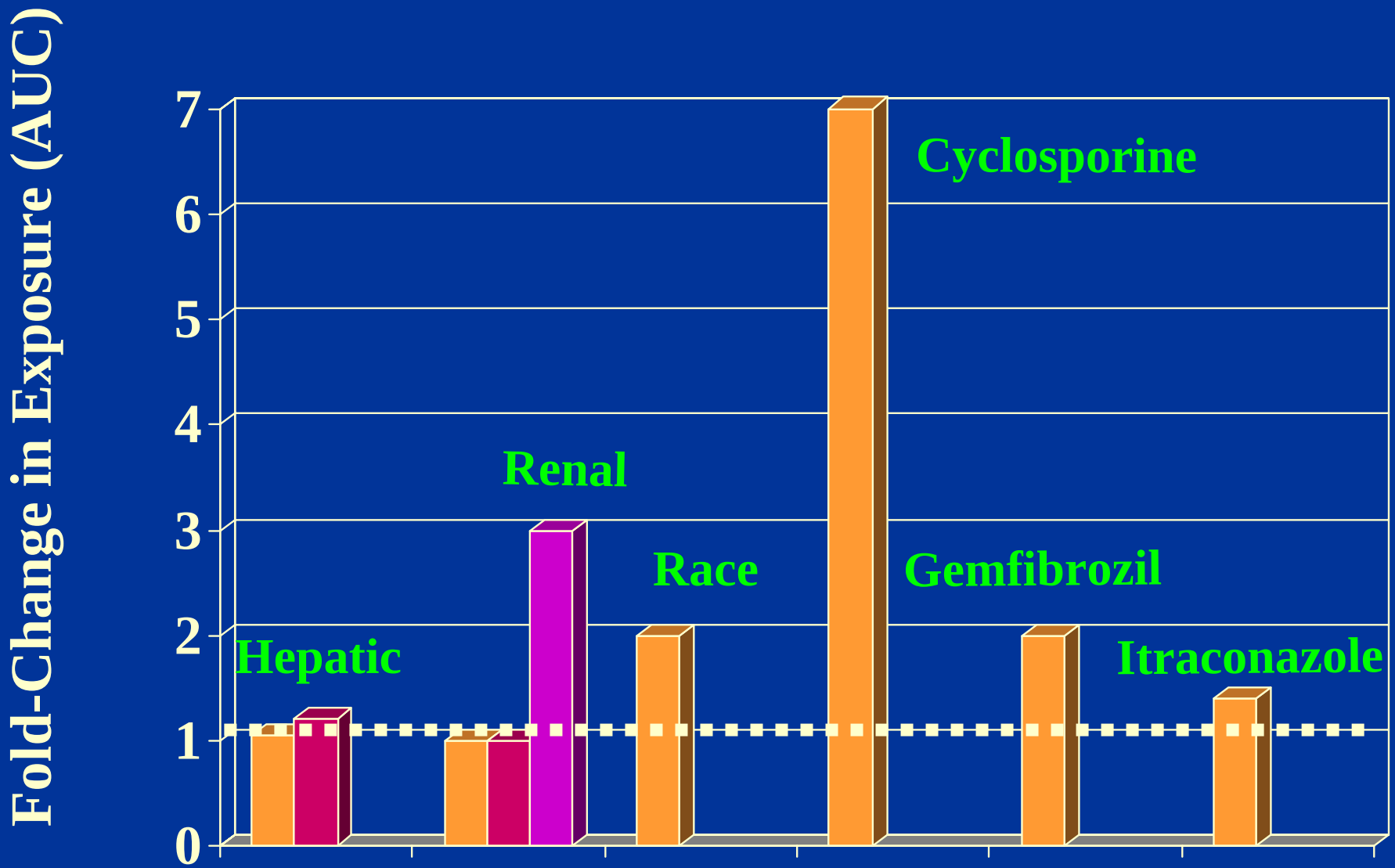
One Aspect of Clinical Pharmacology and Biopharmaceutics Review



Dosage adjustment for specific populations with *extrinsic* and *intrinsic* factors

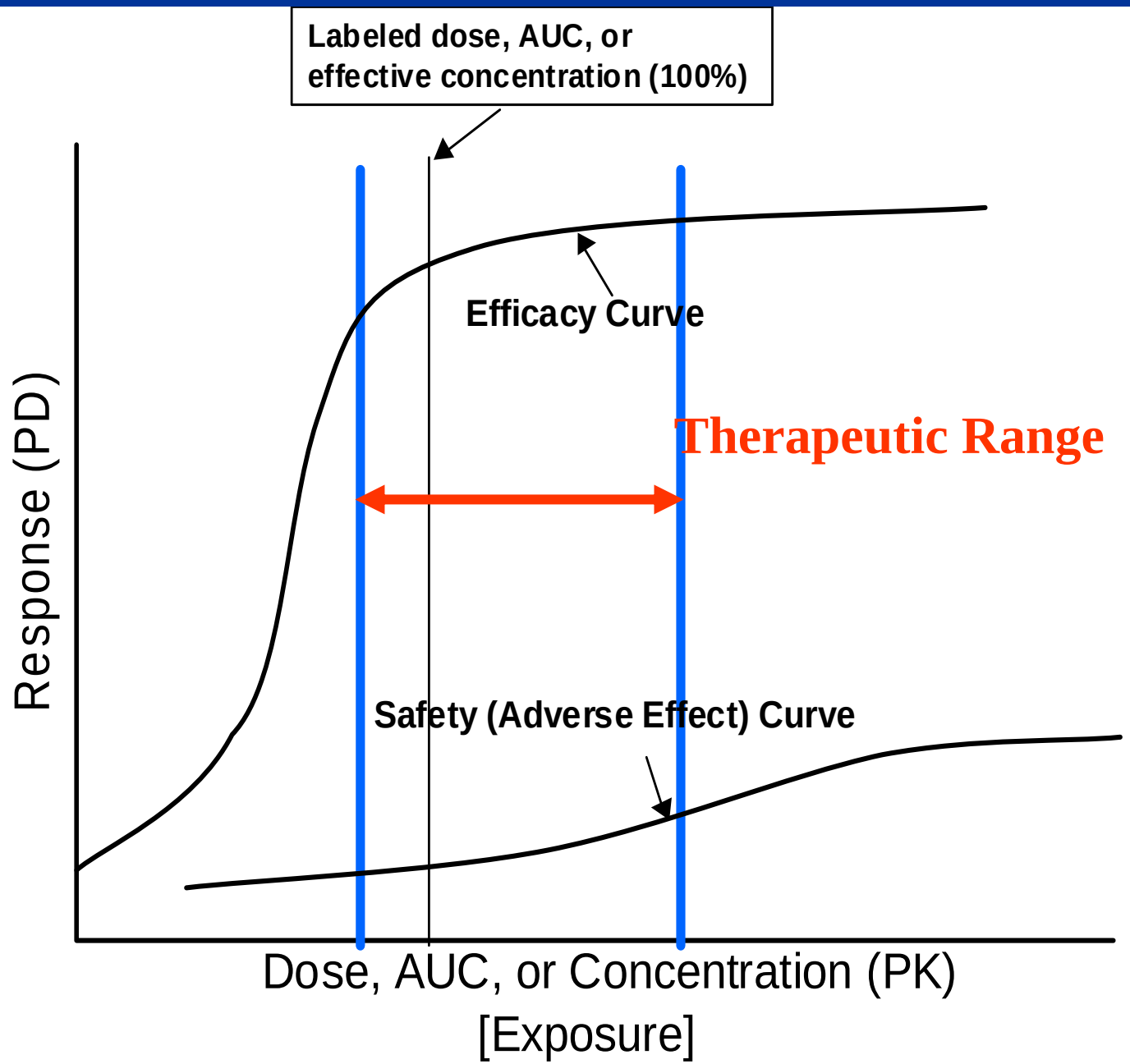
Adapted from ICH E5, 1998: http://www.fda.gov/cder/guidance/2293fnl.pdf

Evaluation of systemic exposure changes in specific populations

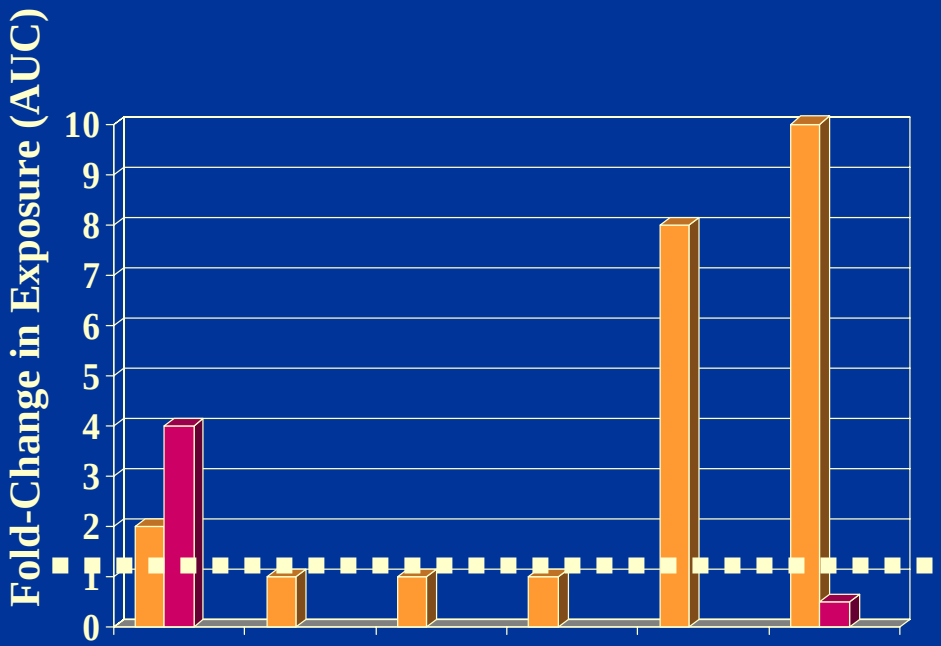


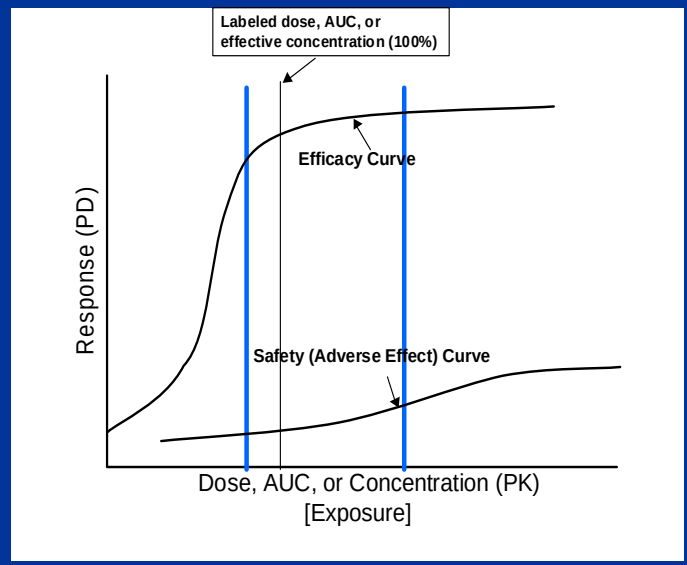
< Data compiled from PDR entry for CRESTOR® (AstraZeneca) (rosuvastatin calcium) labeling>

Establishment of exposure - response relationship



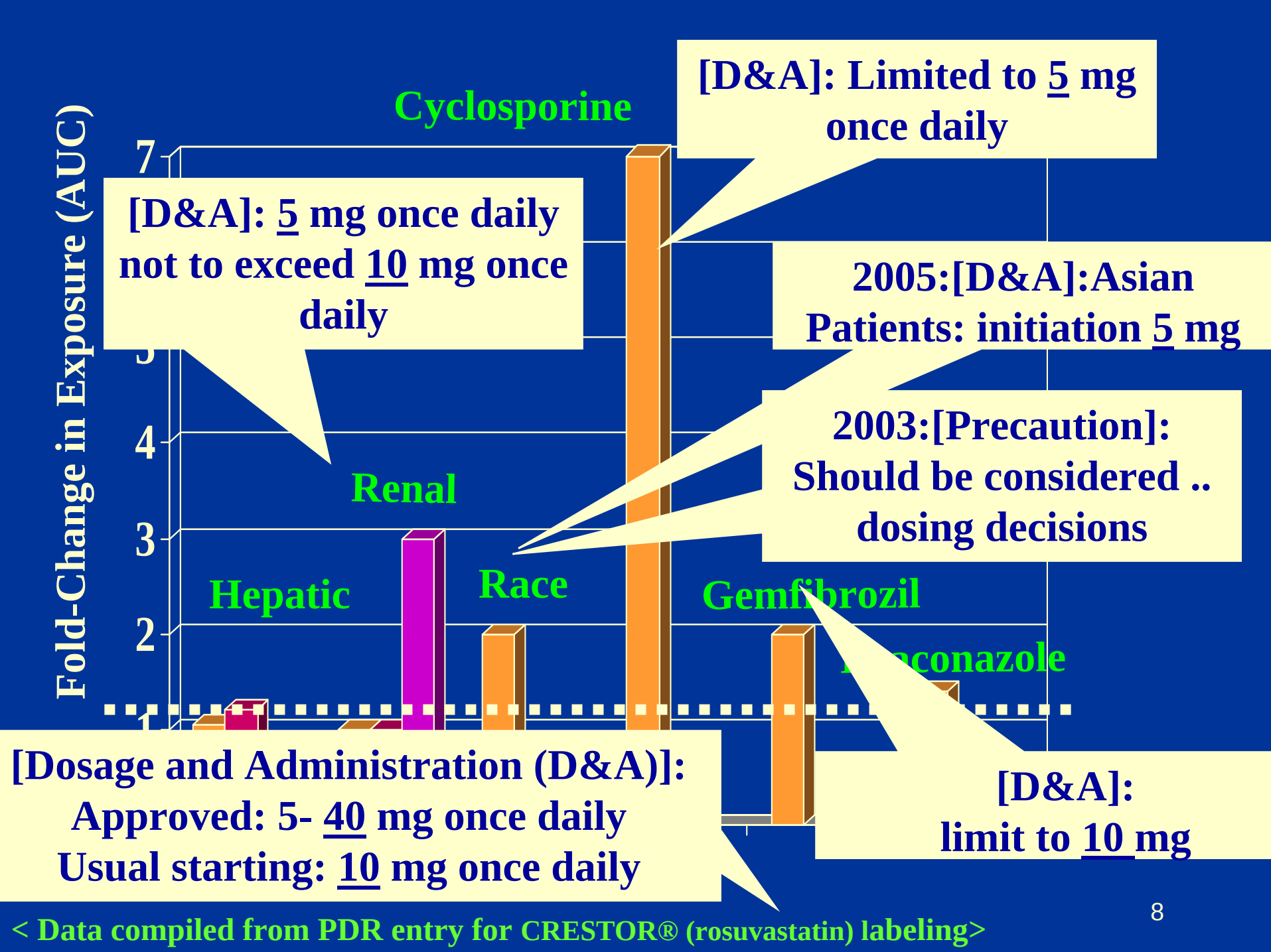
< Huang and Lesko, J Clin Pharmacol, 44: 559. June 2004>





Labeling recommendations

Other considerations



< Data compiled from PDR entry for CRESTOR® (rosuvastatin) labeling>

Evaluation of drug interactions critical to risk/benefit assessment

Recent US Market Withdrawal (1998-2003) **

Withdrawn	Approval	Drug name	Use	Risk
1998	1997	Mibefradil	High blood pressure/ Chronic stable angina	Drug-drug interactions Torsades de Pointes
1998	1997	Bromfenac	NSAID	Acute liver failure
1998	1985	Terfenadine	Antihistamine	Torsades de Pointes Drug-drug interactions
1999	1988	Astemizole	Antihistamine	Torsades de Pointes Drug-drug interactions
1999	1997	Grepafloxacin	Antibiotics	Torsades de Pointes
2000	2000	Alosetron*	Irritable bowel syndrome in women	Ischemic colitis; complications of constipation
2000	1993	Cisapride	Heartburn	Torsades de Pointes Drug-drug interactions
2000	1997	Troglitazone	Diabetes	Acute liver failure
2001	1997	Cerivastatin	Cholesterol lowering	Rhabdomyolysis Drug-drug interactions
2001	1999	Rapacuronium	Anesthesia	Bronchospasm

*Reintroduced in 2001; ** rofecoxib (Vioxx) withdrawn in Sept 2004; natalizumab (Tysabri) withdrawn in Feb 2005

<Table from Huang SM, Miller M, Toigo T, Chen MC, Sahajwala C, Lesko LJ, Temple R, Evaluation of Drugs in Women: Regulatory Perspective– in Section 11, Drug Metabolism/Clinical Pharmacology (section editor: Schwartz, J), in "Principles of Gender-Specific Medicine", Ed., Legato M, Academic Press (2004) >

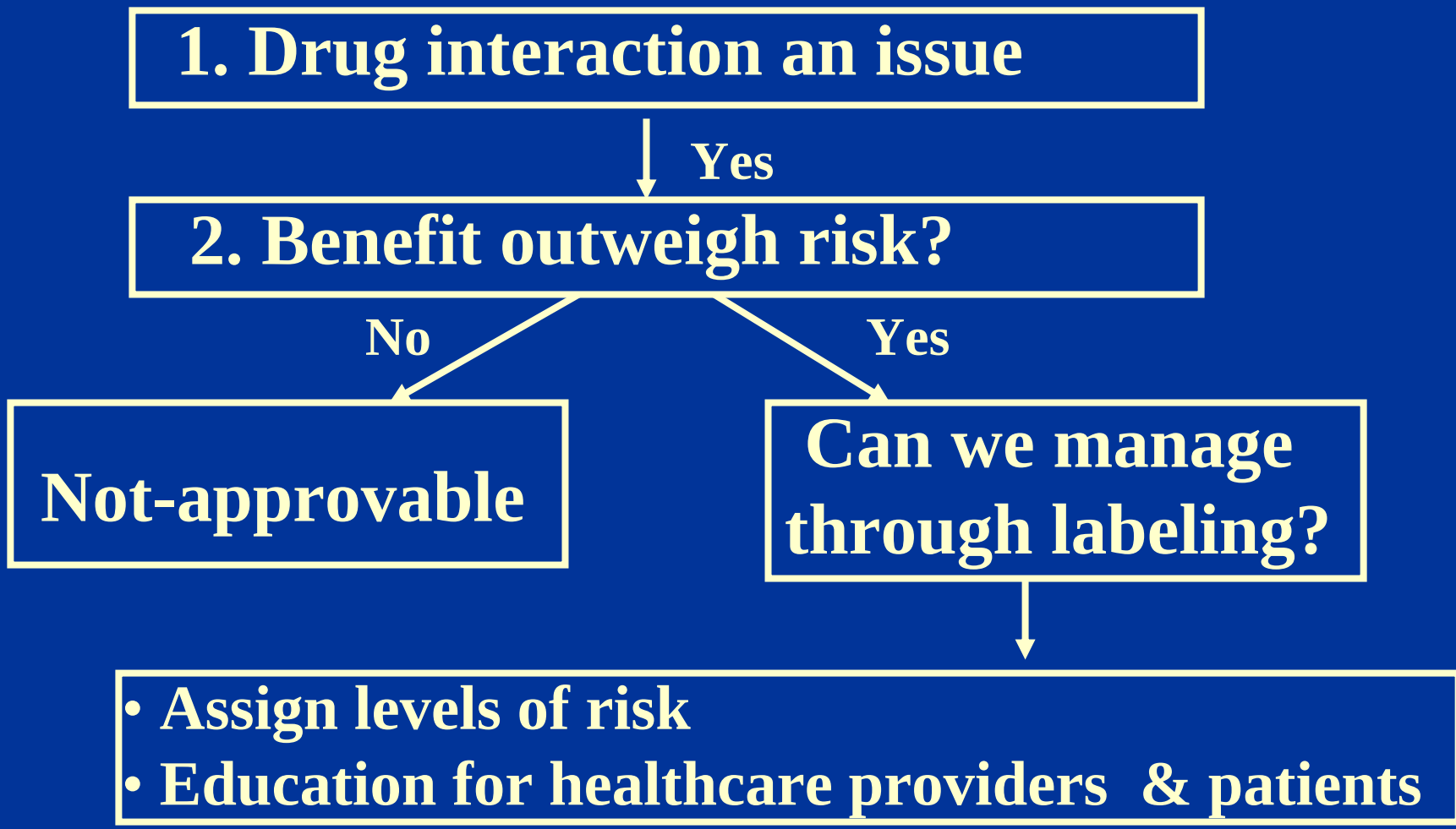
“…drug interactions represent 3-5% of preventable ADRs and are an important contributor to ER visits and hospital admissions.”

< JAMA 1995;274(1):35–43>

“…elderly patients with digoxin toxicity were 12 times more likely to have been treated with clarithromycin”

< JAMA 2003;289 (13):1652>

What lessons have we learned? Questions to ask when review NDA/ Post-marketing data



< Lesko, L, et al, QA/QC Report, 2000; Huang S-M, et al, Clin Pharmacol Ther 2000; 67(2): 148; Huang, S-M, Drug-drug interactions, in « Applications of Pharmacokinetic Principles in Drug Development », Ed. Rajesh Krishina, Kluwer Academic/Plenum Publishers, 2003 >

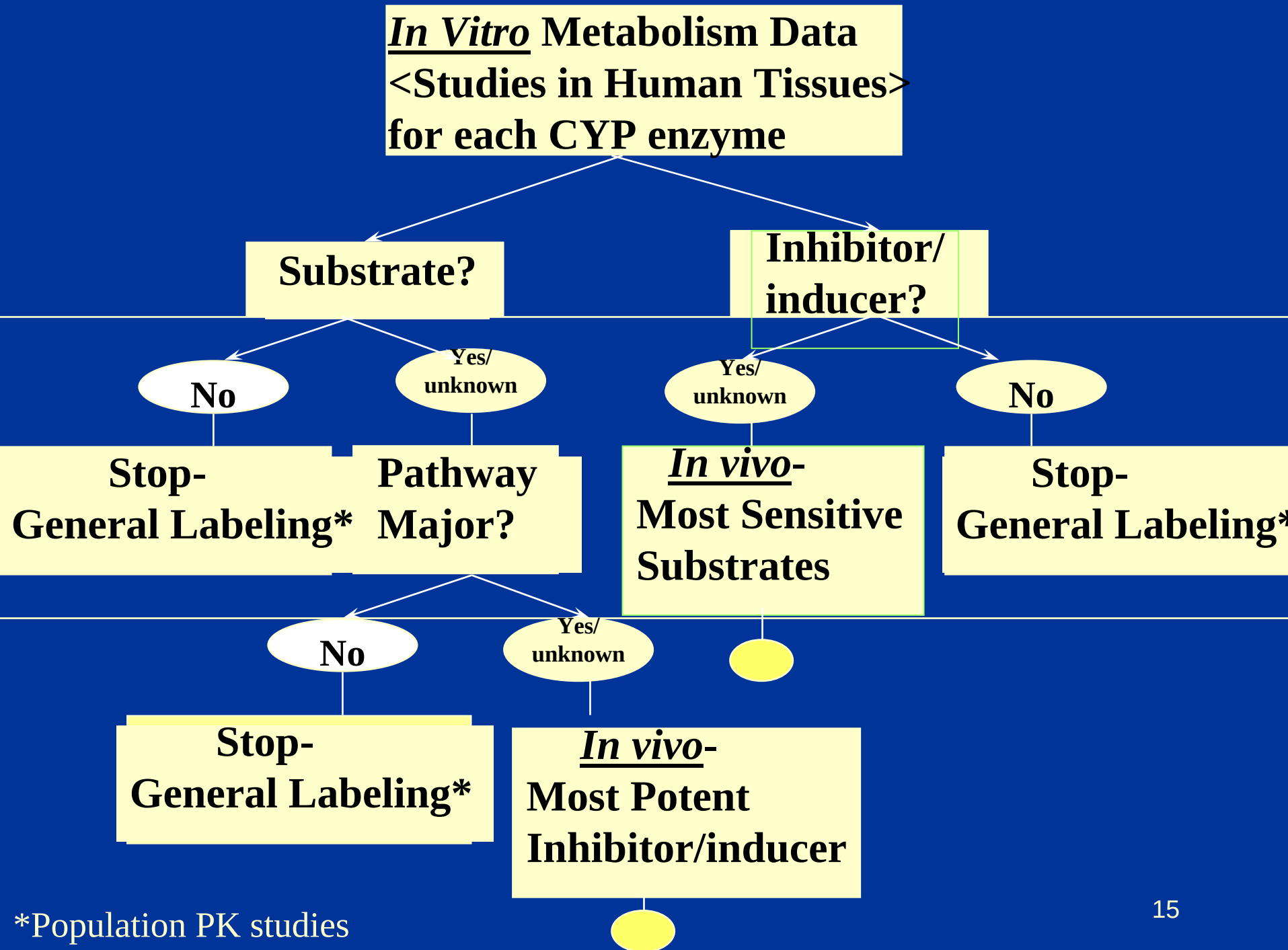
Concept Paper

Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling

FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 3, 2004;
http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm;
http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm
http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4079T1.htm

Key Messages:

1. Metabolism, drug-interaction info key to benefit/risk assessment
2. Integrated approach may reduce number of unnecessary studies and optimize knowledge
3. Study design/data analysis key to important information for proper labeling
4. Need to establish “Therapeutic equivalence boundaries”
5. Labeling language needs to be useful and consistent



*Population PK studies

Evaluation of metabolic interactions

Inhibition	**CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A, CYP2D6**
Induction	**CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A**
Metabolic Profiling	**CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A, CYP2D6**
	Other CYPs/Phase 2 metabolism

Evaluation of inhibition

"The likelihood of an in vivo interaction is projected based on the [I]/Ki ratio where [I] represents the mean steady-state Cmax value for total drug (bound plus unbound) following administration of the highest proposed clinical dose. As the ratio increases, the likelihood of an interaction increases."

Prediction of clinical relevance of competitive CYP inhibition

I/Ki	***Prediction***
I/Ki > 1	***Likely***
1> I/Ki> 0.1	***Possible***
0.1> I/Ki	***Remote***

An estimated I/Ki ratio of greater than 0.1 is considered positive and a follow-up in vivo evaluation is recommended.

Evaluation of inhibition

Design the *in vivo* evaluation based on *in vitro* data

- **Initial prediction based on I/Ki**
- **rank order and evaluate the more potent ones, smaller Kis, first or largest I/Ki**

NME (Cmax 2uM)

	IC50	Ki	I/Ki
CYP1A2	**50 uM**	**20 uM**	**0.1**
CYP2C8	**>100 uM**	**--**	
CYP2C9	**>100 uM**	**--**	
CYP2C19	**>100 uM**	**--**	
CYP2D6	**>100 uM**	**--**	
CYP3A4	**7uM**	**2 uM**	**1**

Evaluate in vivo first

In vivo probes

CYP	Substrate	Inhibitor	Inducer
1A2	theophylline, caffeine	fluvoxamine	smoking[3] *NEW!*
2B6	efavirenz		rifampin
2C8	repaglinide, rosiglitazone	gemfibrozil	rifampin
2C9	warfarin, tolbutamide	fluconazole, amiodarone (use of PM subjects) [4] *NEW!*	rifampin
2C19	omeprazole, esoprazole, lansoprazole, pantoprazole	omeprazole, fluvoxamine, moclobemide (use of PM subjects) [4] *NEW!*	rifampin
2D6	desipramine, atomoxetine dextromethorphan	paroxetine, quinidine, (use of PM subjects) [4] *NEW!*	None identified
2E1	chlorzoxazone	disulfirum	ethanol
3A4/ 3A5	midazolam, buspirone, felodipine, simvastatin, lovastatin, eletriptan, sildenafil, simvastatin, triazolam, vardenafil	atanazavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole	rifampin, carbamazepine

** To be posted on internet; updated regularly*

Do we have a similar system well developed for evaluation of transporter-based interactions?

Table. Drug interactions due to inhibition of transport proteins

Substrate	Inhibitor	Transporter
digoxin	quinidine, verapamil, itraconazole	P-gp; OATP
fexofenadine	ketoconazole, erythromycin, azithromycin	P-gp; OATP
talinolol	verapamil	P-gp
loperamide	quinidine	P-gp
dofetilide procainamide levofloxacine	cimetidine	OCT;OAT; OATP
penicillins ACE inhibitors Antiviral drugs	probenecid	OAT
paclitaxel	valspodar	P-gp

P-gp: p-glycoprotein; OAT: organic anion transporter; OCT: organic cation transporter: OATP: organic anion transport protein

< Adapted from PhRMA white paper, Bjonrsson, et al, Drug Metab Dispos July 2003 and J Clin Pharmacol, May 2003 >

FDA Advisory Committee for Pharmaceutical Sciences - Clinical Pharmacology Subcommittee meeting: Drug interaction concept paper Rockville, MD November 3, 2004

http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm;
http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm
http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4079T1.htm

Questions associated with *inhibition* of transporters (1)

If a NME IS an *inhibitor* of P-gp in vitro, then there IS a need to conduct an in vivo study using digoxin or other suitable substrates.

Yes or No

If a NME IS a *substrate* for P-gp in vitro AND a CYP3A4 substrate based on either in vitro and/or in vivo data, then a clinical study with a P-gp- and CYP3A4-inhibitor (e.g., ritonavir) should be conducted.

Yes or No

Questions associated with *inhibition* of transporters (2)

If a NME IS a *substrate* for P-gp in vitro AND NOT a CYP3A4 substrate based on either in vitro and/or in vivo data, then a clinical study with a P-gp-inhibitor (e.g., cyclosporine, verapamil) should be conducted.

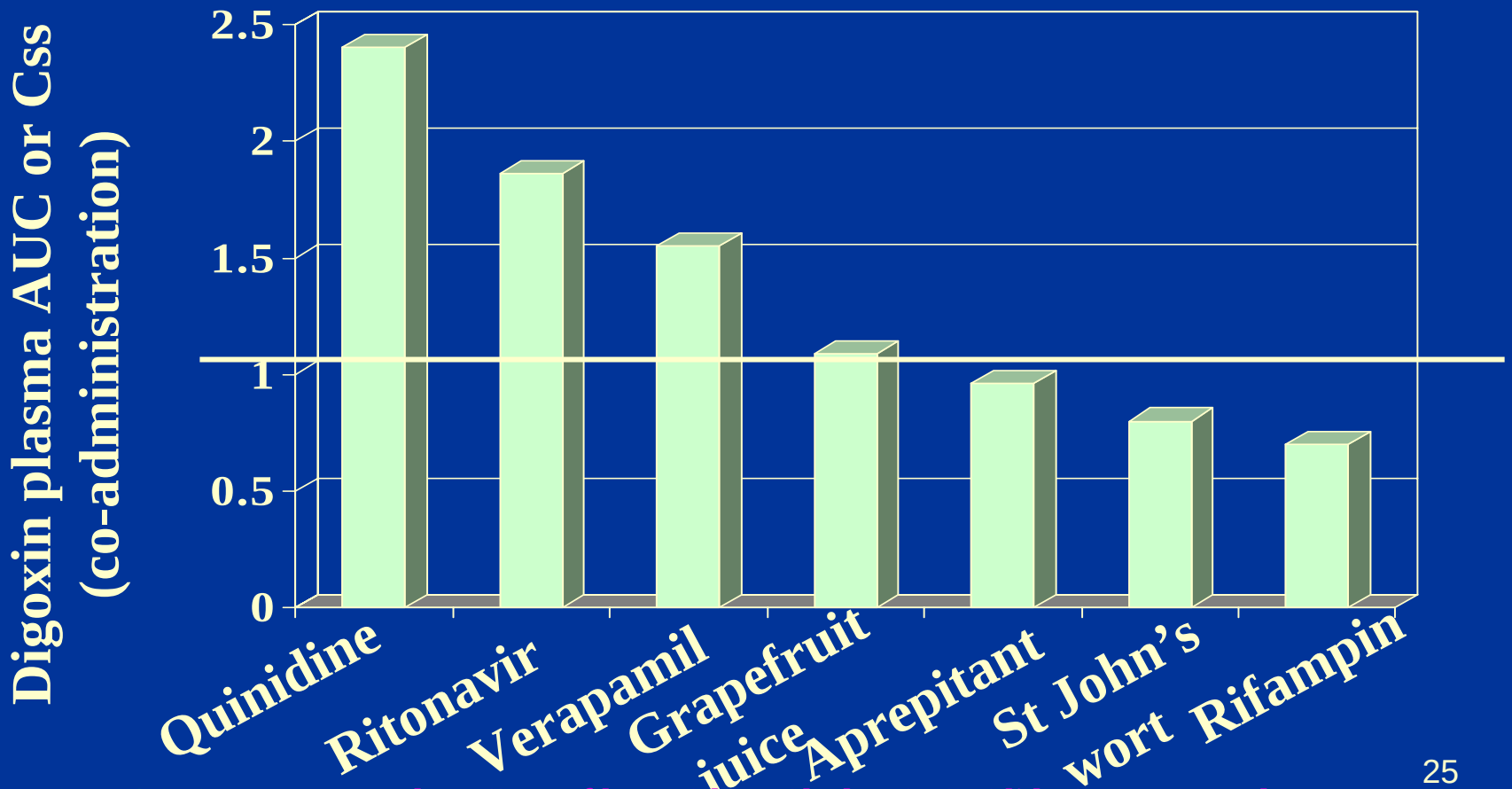
Yes or No

Does the current evidence support recommendations that drug-drug interactions based on OATP and/or MRP be recommended for clinical study during drug development?

Yes or No

P-gp transporter based interaction (1)

If a NME is an inhibitor of P-gp in vitro, in vivo study using digoxin may be appropriate



Huang, S-M, ACPS presentation, , http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm

P-gp transporter based interaction (2)

If a NME is a substrate for <u>P-gp and CYP3A</u>
-> a clinical study with a multi- inhibitor (e.g., ritonavir) may be appropriate

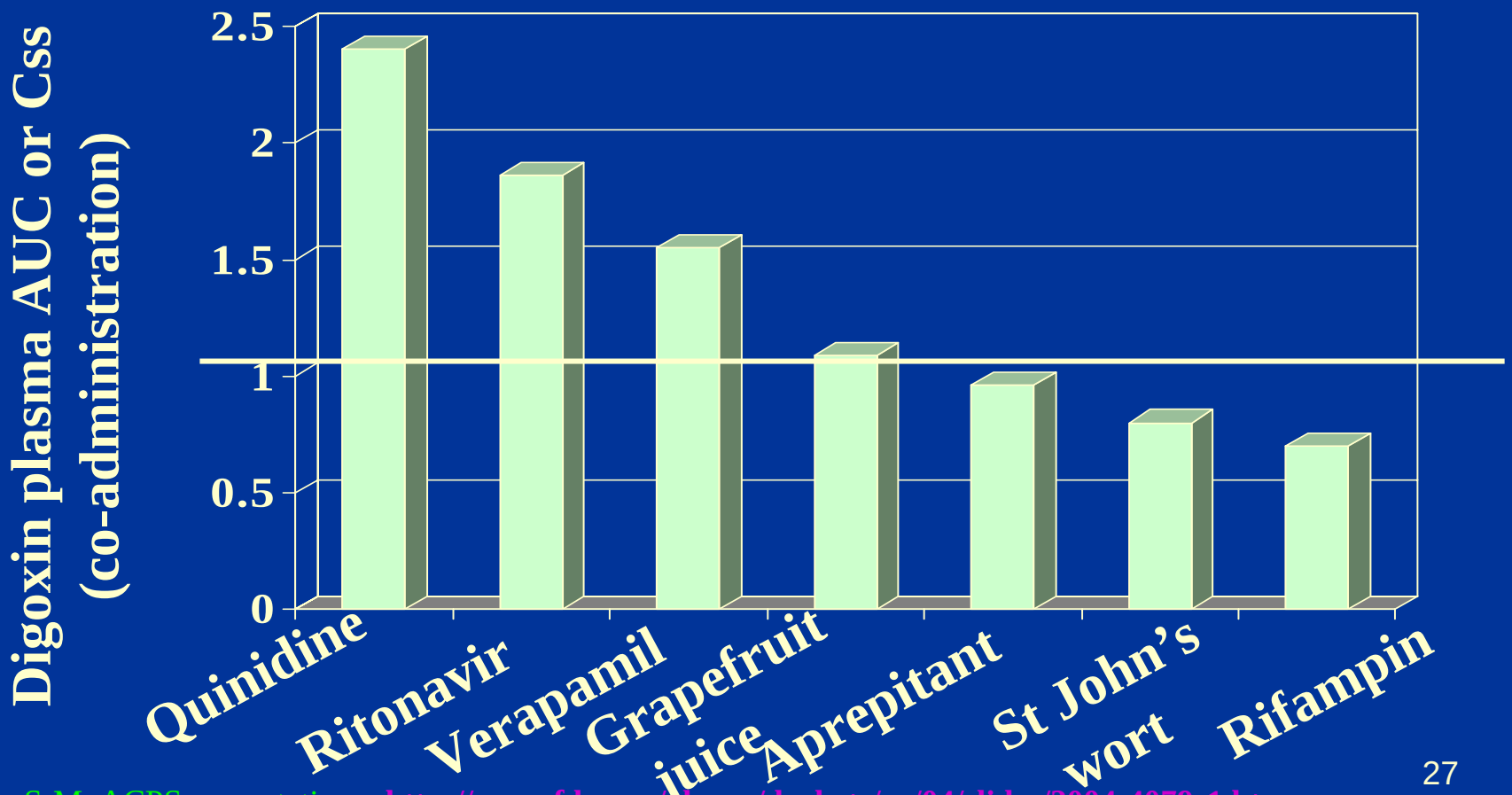
[Ritonavir affects multiple pathways]

Huang, S-M, ACPS presentation, , http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm

P-gp transporter based interaction (3)

If a NME is a substrate for <u>P-gp and NOT CYP3A4</u>

-> a clinical study with a P-gp- inhibitor (e.g., cyclosporine, verapamil) may be appropriate



Huang, S-M, ACPS presentation, , http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm

No general agreement on these approaches

- In vitro (pre- clinical) methods not standardized/readily available
- Quantitative in vitro prediction of in vivo relevance not possible
- In vivo data not generalizable

FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 3, 2004; http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4079T1.htm

P-gp -

- Digoxin a suitable probe substrate
- No good P-gp inhibitors available

  - pitfalls in using ritonavir, verapamil, cyclosporine

Other transporters

- in vitro tools far less standardized/available
- Few defined substrates/inhibitors available
- data not generalizable to broader clinical practice

Taken from Gottesdiener, K, ACPS presentation, November 3, 2004, http://www.fda.gov/ohrms/dockets/ac/04/transcripts/2004-4079T1.htm

“Class” labeling of drugs that are substrates of CYP3A

Labeling

If a drug has been determined to be a sensitive CYP3A *substrate* or a CYP3A *substrate* with a narrow therapeutic range, it does not need to be tested with all strong or moderate inhibitors of CYP3A to warn about an interaction with "strong" or "moderate" CYP3A inhibitors

FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 3, 2004; http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm; http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm; Huang, S-M, presentation

Examples of strong and moderate CYP3A inhibitors

Strong CYP3A inhibitors	Moderate CYP3A inhibitors
atanazavir clarithromycin indinavir itraconazole ketoconazole nefazodone nelfinavir ritonavir saquinavir telithromycin voriconazole	amprenavir aprepitant diltiazem erythromycin fluconazole fosaprenavir *grapefruit juice(a)* verapamil

A "strong inhibitor" is one that caused a ≥ 5-fold increase in the plasma AUC values of CYP3A substrates (not limited to midazolam) in clinical evaluations

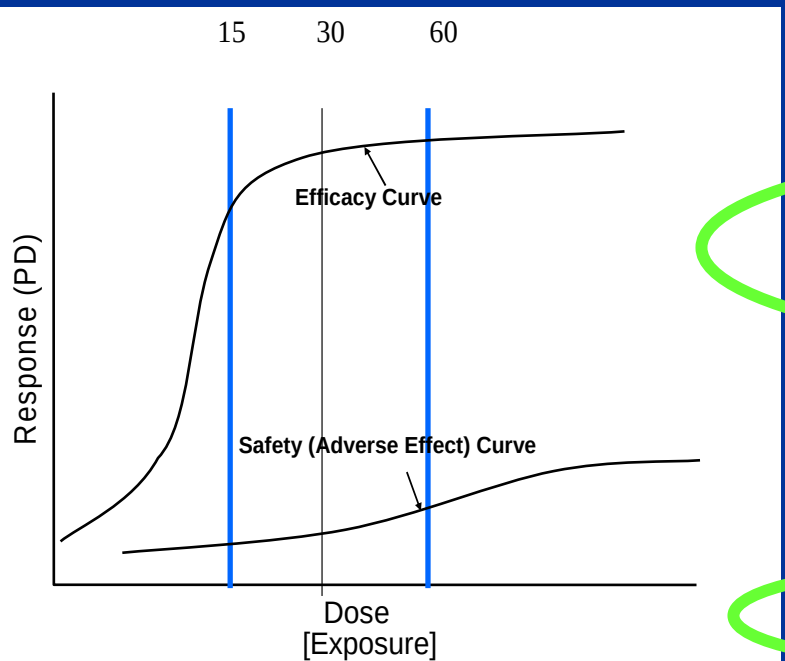
A "moderate inhibitor" is one that caused a ≥ 2- but < 5-fold increase in the AUC values of sensitive CYP3A substrates when the inhibitor was given at the highest approved dose and the shortest dosing interval in clinical evaluations

(a) The effect varies widely

Labeling example - CYP3A substrate

Drug with	Drug AUC	Drug Cmax
Ketoconazole	8x	4x
Erythromycin	6x	3x
Verapamil	5x	3x

[if approved]



Do not take with strong CYP3A inhibitors….
Ketoconazole, itraconazole, ritonavir, nelfinavir, nefazodone, clarithromycin.

Use lower dose with moderate CYP3A inhibitors…..
erythromycin, verapamil, diltiazem...

Not studied

Do we have sufficient data for “class” labeling of drugs that are substrates of transporters?

“Class” labeling of drugs that are inhibitors of CYP3A

Labeling

If a drug has been determined to be a strong *inhibitor* of CYP3A, it does not need to be tested with all CYP3A substrates to warn about an interaction with "sensitive CYP3A substrates" and "CYP3A substrates with narrow therapeutic range".

FDA Advisory Committee for pharmaceutical sciences and Clinical Pharmacology Subcommittee meeting. Issues drug interaction concept paper. Rockville, MD. November 3, 2004; http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4079b1.htm; http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4079s1.htm; Huang, S-M, presentation

Examples of sensitive CYP3A substrates or CYP3A substrates with NTR

Sensitive CYP3A substrates	CYP3A Substrates with Narrow therapeutic range
budesonide, buspirone, eletriptan, felodipine, imatinab, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam, vardenafil	Alfentanil, astemizole(a), cisapride(a), cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine(a)

"sensitive CYP3A substrates" refer to drugs whose plasma AUC values are increased 5-fold or more when co-administered with CYP3A inhibitors

"CYP3A substrates with narrow therapeutic range" refer to drugs whose exposure-response data are such that increases in their exposure levels by the concomitant use of CYP3A inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes);

(a) not available in US

Labeling example- CYP3A inhibitor

Telithromycin	AUC
Midazolam	6x

- Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system
- Use of simvastatin, lovastatin, or atorvastatin concomitantly with KETEK should be avoided
- The use of KETEK is contraindicated with cisapride, pimozide

Not studied

<Pysicians' Desk Reference at http://pdrel.thomsonhc.com/pdrel/librarian >

Do we have sufficient data for “class” labeling of drugs that are inhibitors of transporters?

Labeling examples

Fexofenadine

These studies indicate that ketoconazole or erythromycin co-administration enhances fexofenadine gastrointestinal absorption. This observed increase in the bioavailability of fexofenadine may be due to *transport-related effects, such as p-glycoprotein*. *In vivo* animal studies also suggest that in addition to enhancing absorption, ketoconazole decreases fexofenadine gastrointestinal secretion, while erythromycin may also decrease biliary excretion.

http://www.fda.gov/cder/foi/label/2004/21704lbl.pdf

Fexofenadine (2)

Interactions with Fruit Juices

Fruit juices such as grapefruit, orange and apple may reduce the bioavailability and exposure of fexofenadine. This is based on the results from 3 clinical studies using histamine induced skin wheals and flares coupled with population pharmacokinetic analysis. …… Therefore, to maximize the effects of fexofenadine, it is recommended that ALLEGRA-D 24 HOUR *should be taken with water*

http://www.fda.gov/cder/foi/label/2004/21704lbl.pdf

Eplerenone

Eplerenone is not a substrate or an inhibitor of *P-glycoprotein* at clinically relevant doses

No clinically significant drug-drug pharmacokinetic interactions were observed when eplerenone was administered with *digoxin*

http://www.fda.gov/cder/foi/label/2003/21437se1-002_inspra_lbl.pdff

Levonorgestrel and Ethinyl Estradiol

Herbal products containing St. John's wort (Hypericum perforatum) may *induce hepatic enzymes* (cytochrome P 450) and *p-glycoprotein transporter* and may reduce the effectiveness of contraceptive steroids. This may also result in breakthrough bleeding .

http://pdrel.thomsonhc.com/pdrel/librarian/PFDefaultActionId/pdrcommon.IndexSearchTranslator#PDRPRE01el/2004/21704lbl.pdf

Pramipexole

Probenecid: **Probenecid, a known inhibitor of renal tubular secretion of organic acids via *the anionic transporter*, did not noticeably influence pramipexole pharmacokinetics (N=12).**

http://pdrel.thomsonhc.com/pdrel/librarian/PFDefaultActionId/pdrcommon.IndexSearchTranslator#PDRPRE01el/2004/21704lbl.pdf

Dofetilide

Dofetilide is eliminated in the kidney by cationic secretion. Inhibitors of *renal cationic secretion* are contraindicated with TIKOSYN. In addition, drugs that are actively secreted via this route (e.g., triamterene, metformin and amiloride) should be co-administered with care as they might increase dofetilide levels.

http://pdrel.thomsonhc.com/pdrel/librarian/PFDefaultActionId/pdrcommon.IndexSearchTranslator#PDRDIA01

Summary

P-gp- based interactions

- Most well developed
- Information increasingly included in labeling
- To determine when to evaluate in vivo:
  need agreed-upon criteria to evaluate
  in vitro (preclinical) data
- Digoxin a clinically relevant substrate
- Need to define specific inhibitors

Other transporter- based interactions

- In vitro methodologies being developed
- Some information has been included in labeling
- Need continued research; need probe substrates/inhibitors
- Short-term recommendations may be drug- or “therapeutic class-” specific

Other considerations- Interplay with other intrinsic and extrinsic factors

Genotypes and Drug Interactions

Substrate (enzyme)	Inhibitor or inducer	Outcome (changes in plasma AUC or concentrations of substrates)	
Atomoxetine (CYP2D6)	fluoxetine, paroxetine	AUC increase 6-8 fold in EM; no change in PM expected	
Metoprolol (CYP2D6)	diphenhydramine	Higher inhibition in EM vs. PM (fold vs. fold)	
Tamoxifen (CYP2D6)	paroxetine	Greater reduction in plasma levels of endoxifen (active metabolite of tamoxifen formed via CYP2D6) in homozygous EM as compared to patients with at least one variant allele	
Diazepam (CYP2C19)	omeprazole	No inhibition in PM	
Omeprazole (CYP2C19)	fluvoxamine	AUC increased 3-6 fold in EM; no changes in PM	
Omeprazole (CYP2C19)	Gingko Biloba	Higher induction in EM	

< Huang, S-M, Lesko, LJ, "Application of Pharmacogenomics in Clinical Pharmacology" - in Part I: Molecular Medicine, Correlation between genes, diseases and biopharmaceuticals, in "Modern Biopharmaceuticals- Design, Development and Optimization", Ed., Jorg Knablein and RH Muller, Wiley, VCH (in press) >

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